Remarks

Claims 1-5, 8-11, 13-18, 37 and 38 are pending and under consideration in the subject application. Applicants have hereinabove cancelled claims 2, 3, 6, 7, 12, 19-36, 39 and 40 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application. Applicants have also amended claims 1 and 4. Support for the amendment to claim 1 may be found, inter alia, in cancelled claim 3. Applicants maintain that none of the changes to the claims raises an issue of new matter. Therefore, entry of this Amendment is respectfully requested.

Formalities

Applicants acknowledge the Examiner's withdrawal of the following rejections:

i) the rejection of claims 1-5, 13-15, 17, and 18 under 35 U.S.C. §102(b) as being anticipated by Stein et al. (1999);

ii) the rejection of claims 1-5, 8-11, 13-18, and 37 under 35 U.S.C. §102(e) as being anticipated by Frankel et al. (US 6,316,03);

iii) the rejection of claims 1-5, 8-11, 13-16, 37, and 38 under 35 U.S.C. §102(e) as being anticipated by Rothbard et al. (US 6,306,993); and

iv) the rejection of claims 1-5, 8-11, 13-18, 37, and 38 under 35 U.S.C. §103 (as) as being obvious over Futaki et al. (February, 2001) in view of Awwad et al. (1994).

The Examiner stated that the following new grounds of rejection

were necessitated by applicants' December 21, 2005 Amendment.

Claim Rejections Under 35 U.S.C. §102(b)

The Examiner rejected claims 1-3, 10, 17, and 18 under 35 U.S.C. §102(b) as allegedly anticipated by Awwad et al. (1994). The Examiner stated that claims 1-3, 10, 17, and 18 are directed to a composition of matter comprising an antibody and a peptide moiety, wherein the peptide moiety comprises an amino acid residue having a nitrogen-containing side chain and wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody. The Examiner asserted that Awwad et al. teach the periodate oxidation of a monoclonal antibody and subsequent conjugation to a peptide linker containing lysine (citing Abstract and Materials and methods, Modification of mAb). The Examiner stated that Awwad et al. point out that carbohydrates are covalently bound primarily to the Fc (CH2 domain) of antibodies (citing page 23, last paragraph, the second sentence).

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants point out that claims 2 and 3 have been cancelled. Thus, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse. Briefly, amended claim 1 provides a composition of matter comprising an antibody and a peptide moiety wherein the peptide comprises L-arginine and is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Awwad et al. teach do not teach a composition of matter

comprising an antibody and a peptide moiety wherein the peptide comprises L-arginine. Thus, Awwad et al. fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claim 1, and claims 10, 17 and 18 which depend therefrom, satisfy the requirements of 35 U.S.C. §102(b). Therefore, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §103

Awwad et al. in view of Futaki et al.

The Examiner rejected claims 1-5, 10, 11 and 13-18 under 35 U.S.C. §103(a) as allegedly unpatentable over Awwad et al. (1994) in view of Futaki et al. (2001).

The Examiner stated that the instant invention is further limited to a composition comprising an antibody covalently bound to a poly-L-arginine peptide of various lengths. The Examiner conceded that Awwad et al. do not teach the poly-L-arginine peptide.

The Examiner asserted that Futaki et al. teach the delivery of exogenous proteins into cells by covalently binding arginine-rich peptides to the protein. The Examiner also asserted that Futaki et al. specifically teach the translocation activity of arginine-rich peptides of 8-27 residues and polyarginine peptides of 4-16 residues (citing page 5837, Figure 1). The Examiner stated that Futaki et al. further point out that eight residues, or an "octa-peptide" as recited in claim 11, would be an optimal number for efficient translocation (citing Abstract).

The Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the lysine peptide moiety of Awwad et al. to the poly-arginine peptide as suggested by Futaki et al. with a reasonable expectation of success since an antibody is an exogenous protein and arginine and lysine both have a nitrogen-containing side chain comprising a guanido group. The Examiner asserted that the motivation to do so is provided by Futaki et al., who teach the efficient translocation activity of various arginine-rich peptides and disclose that the arginine-based peptides seem to have great cell membrane penetration ability, which would be advantageous for intracellular protein delivery (citing last paragraph). The Examiner concluded that the claimed invention as a whole is prima facie obvious over Awwad et al. in view of Futaki et al.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants point out that claims 2 and 3 have been cancelled. Thus, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Again, amended claim 1 provides a composition of matter comprising an antibody and a peptide moiety comprising arginine wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Here, the cited references fail to support a prima facie case of

obviousness. Specifically, Awwad et al., when combined with Futaki et al., fail to provide a motive to combine them.

Awwad et al. disclose site-specific attachment of a metal chelator and a cytotoxic agent to the carbohydrate moiety of an antibody. Nowhere is it suggested that such attachment could be used to attach a peptide comprising arginine to an antibody.

Futaki et al. teach intracellular delivery of carbonic anhydrase which was covalently conjugated with arginine-rich peptides of varying lengths. However, this reference does not suggest making a composition comprising an antibody having a peptide covalently bound to a carbohydrate moiety on a CH2 domain of the antibody. Nowhere is it suggested that such a method could be used for making such a composition. In fact, applicants were the first to demonstrate that a 150,000 - 160,000 molecular weight protein molecule covalently bound to an arginine-containing peptide could be transported into a cell.

Contrary to the Examiner's assertion that it would have been obvious to one of ordinary skill in the art at the time that invention was made to modify the lysine peptide moiety of Awwad et al. to the polyarginine peptide used in Futaki et al. because arginine and lysine both have a nitrogen-containing side chain containing a guanido group, applicants note the following. First, lysine does not have a guanido group; only arginine does. Second, there is no suggestion in Awwad et al. that the lysine moiety of the peptide chelator is the site where the reaction occurs. In fact, the second compound used in Awwad et al., doxorubicin, does not contain any amino acids. Therefore, there is no teaching in Awwad et al. that lysine is the site of reaction. Finally, applicants note that neither Awwad et al. nor Futaki et al.

suggest modifying the lysine moiety of Awwad et al. to an arginine moiety.

To support a case of *prima facie* obviousness, Futaki et al., and Awwad et al., when combined, would have to teach or suggest all elements of the rejected claims. Moreover, there would have to have been a motive to combine them, and a reasonable expectation of the invention's success at the time of the invention. Again, one element of each rejected claim is the covalent attachment of a peptide comprising arginine to a carbohydrate moiety on a CH2 domain of the antibody. Thus, at the very least, these references, when combined, would have to teach or suggest this element.

This they fail to do. In addition, and consequently, there is simply no motivation or suggestion to combine the references to create the instant invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' specification. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1, 4, 5, 10, 11, and 13-18 over these references. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over Futaki et al. and Awwad et al.

Awwad et al. in view of Frankel et al.

The Examiner rejected claims 1-5, 8-11, 13-18 and 37 under 35 U.S.C. §103(a) as allegedly unpatentable over Awwad et al., in

view of Frankel et al. (U.S. 6,316,003).

The Examiner stated that these claims are drawn to the above-mentioned composition with further limitations of molecular weight, 13 kD, within the range between 11 kD and 16 kD, and of being combined with a pharmaceutically acceptable carrier in a pharmaceutical composition.

The Examiner conceded that Awwad et al. do not teach these further limitations.

The Examiner asserted that Frankel et al. teach the use of transport peptides to deliver cargo molecules, particularly, an antibody (citing columns 115 and 116, claims 1 and 6). The Examiner asserted that the reference discloses transport peptides such as portions of HIV Tat protein (citing column 3, lines 21-31, and SEQ ID NOs: 1-7). The Examiner asserted that the reference also teaches pharmaceutical, prophylactic and diagnostic compositions comprising transport polypeptide-cargo conjugates (citing column 3, lines 13-20; column 10, lines 66-67; column 11, lines 1-19).

The Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the lysine peptide moiety of Awwad et al. to the poly-arginine peptide as suggested by Frankel et al. with a reasonable expectation of success since arginine and lysine both have a nitrogen-containing side chain comprising a guanido group. The Examiner stated that the motivation to combine is provided when Frankel et al. teach the targeting specificity of these peptides for delivering an antibody into the cell nucleus (col. 12, lines 11-15). The Examiner concluded that the claimed

invention as a whole is *prima facie* obvious over Awwad et al. in view of Frankel et al.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants point out that claims 2 and 3 have been cancelled. Thus, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Again, amended claim 1 provides a composition of matter comprising an antibody and a peptide moiety comprising arginine wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Here, the cited references fail to support a prima facie case of obviousness. Specifically, Awwad et al., when combined with Frankel et al., fail to provide a motive to combine them.

As discussed above, Awwad et al. disclose site-specific attachment of a metal chelator and a cytotoxic agent to the carbohydrate moiety of an antibody. Nowhere is it suggested that such attachment could be used to attach a peptide comprising arginine to an antibody.

Frankel et al. teach a conjugate comprising an antibody and an HIV Tat fragment made by a different method than the method described in the subject specification. Frankel et al. describe reacting an antibody with excess sulfo-SMCC and then adding the HIV Tat fragment, whereas the subject specification describes

reacting an antibody with sodium periodate and then linking the peptide via Schiff base formation. Frankel et al. do not teach whether the reaction described therein causes the HIV Tat fragment to bind to a carbohydrate moiety on the CH2 domain of the antibody or some other domain of the antibody. Therefore, Frankel et al. do not teach, either explicitly or inherently, a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Contrary to the Examiner's assertion that it would have been obvious to one of ordinary skill in the art at the time that the invention was made to modify the lysine peptide moiety of Awwad et al. to the polyarginine peptide as suggested by Frankel et al. because arginine and lysine both have a nitrogen-containing side chain containing a guanido group, applicants again note the following. First, lysine does not have a guanido group; only arginine does. Second, there is no suggestion in Awwad et al. that the lysine moiety of the peptide chelator is the site where the reaction occurs. In fact, the second compound used in Awwad et al., doxorubicin, does not contain any amino acids. Therefore, there is no teaching in Awwad et al. that lysine is the site of reaction. Finally, applicants note that neither Awwad et al. nor Frankel et al. suggest modifying the lysine moiety of Awwad et al. to an arginine moiety.

To support a case of *prima facie* obviousness, Frankel et al., and Awwad et al., when combined, would have to teach or suggest all elements of the rejected claims. Moreover, there would have to have been a motive to combine them, and a reasonable expectation of the invention's success at the time of the invention. Again, one element of each rejected claim is the covalent attachment of

a peptide comprising arginine to a carbohydrate moiety on a CH2 domain of the antibody. Thus, at the very least, these references, when combined, would have to teach or suggest this element.

This they fail to do. In addition, and consequently, there is simply no motivation or suggestion to combine the references to create the instant invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' specification. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1, 4, 5, 8-11, 13-18 and 37 over these references. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over Frankel et al. and Awwad et al.

Awwad et al. in view of Rothbard et al.

The Examiner rejected claims 1-5, 8-11, 13-18, 37 and 38 under 35 U.S.C. §103(a) as allegedly unpatentable over Awwad et al., in view of Rothbard et al. (US 6,306,993).

The Examiner stated that these claims are drawn to the above-mentioned composition combined with a pharmaceutically acceptable carrier in a pharmaceutical composition in a kit.

The Examiner conceded that Awwad et al. do not teach the arginine peptide moiety and the combination with a pharmaceutically acceptable carrier in a pharmaceutical

composition.

The Examiner asserted that Rothbard et al. teach compositions of transport-enhancing polymers containing guanidino side chains (citing the abstract, particularly, column 2, lines 45-67), specifically, poly-arginine polypeptides (column 3, lines 16-25), covalently attached to a biologically active agent for enhanced transport (citing abstract and columns 9-10), which reads on the limitations of claims 1-5 and 37. The Examiner stated that the reference further discloses sequences of transport peptides consisting of 4, 5, 6, 7, 8, 9, 15, 20, 25 and 30 L-arginine polymers, and a mixture of longer L-arginine polymers of up to 100 amino acids, with an average molecular weight of 12,000 Daltons (column 12, lines 1-9; columns 31-34), which reads on the different molecular weights and peptide lengths as recited in claims 8-11, and 13-16. The Examiner also asserted that the reference discloses that the composition may additionally be packaged with instructions for using it (column 4, lines 36-38), which reads on "a kit comprising the composition of claim 1 and instructions for use" as recited in claim 38.

The Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the inventions was made to replace the lysine peptide moiety of Awwad et al. to the poly-arginine peptide as suggested by Rothbard et al. with a reasonable expectation of success since arginine and lysine both have a nitrogen-containing side chain comprising a guanido group. The Examiner stated that the motivation to do so is provided by Rothbard et al., who teach that the use of naturally occurring L-amino acid residues in the transport polymers has the advantage that breakdown products should be relatively non-

toxic to the cell or organism (column 8, lines 26-34). The Examiner concluded that the claimed invention as a whole is *prima facie* obvious over Awwad et al. in view of Rothbard et al.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants point out that claims 2 and 3 have been cancelled. Thus, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Again, amended claim 1 provides a composition of matter comprising an antibody and a peptide moiety comprising arginine wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Here, the cited references fail to support a prima facie case of obviousness. Specifically, Awwad et al., when combined with Rothbard et al., fail to provide a motive to combine them.

As discussed above, Awwad et al. disclose site-specific attachment of a metal chelator and a cytotoxic agent to the carbohydrate moiety of an antibody. Nowhere is it suggested that such attachment could be used to attach a peptide comprising arginine to an antibody.

Rothbard et al. teach attachment of transport molecules to single-chain variable region fragments of antibodies (scFv). However, this reference does <u>not</u> teach a composition of matter comprising an antibody and a peptide moiety wherein the peptide

is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody. Applicants note that variable region fragments (scFv) of antibodies are distinct from the constant region fragments (CH2) described by applicants (see Exhibit A of applicants' December 21, 2006 response). Therefore, Rothbard et al. do not teach, either explicitly or inherently, a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Contrary to the Examiner's assertion that it would have been obvious to one of ordinary skill in the art at the time that invention was made to modify the lysine peptide moiety of Awwad et al. to the polyarginine peptide as suggested by Rothbard et al. because arginine and lysine both have a nitrogen-containing side chain containing a guanido group, applicants again note the following. First, lysine does not have a guanido group; only arginine does. Second, there is no suggestion in Awwad et al. that the lysine moiety of the peptide chelator is the site where the reaction occurs. In fact, the second compound used in Awwad et al., doxorubicin, does not contain any amino acids. Therefore, there is no teaching in Awwad et al. that lysine is the site of reaction. Finally, applicants note that neither Awwad et al. nor Rothbard et al. suggest modifying the lysine moiety of Awwad et al. to an arginine moiety.

To support a case of *prima facie* obviousness, Rothbard et al., and Awwad et al., when combined, would have to teach or suggest all elements of the rejected claims. Moreover, there would have to have been a motive to combine them, and a reasonable expectation of the invention's success at the time of the invention. Again, one element of each rejected claim is the

covalent attachment of a peptide comprising arginine to a carbohydrate moiety on a CH2 domain of the antibody. Thus, at the very least, these references, when combined, would have to teach or suggest this element.

This they fail to do. In addition, and consequently, there is simply no motivation or suggestion to combine the references to create the instant invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' specification. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1, 4, 5, 8-11, 13-18, 37 and 38 over these references. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over Rothbard et al. and Awwad et al.

In view of the above remarks, applicants maintain that claims 1, 4, 5, 8-11, 13-18, 37 and 38 satisfy the requirements of 35 U.S.C. §103(a).

Summary

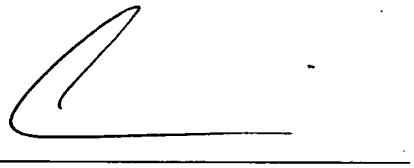
In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing

prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. If any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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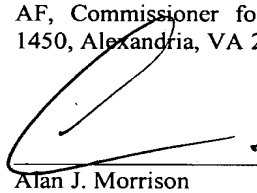

5/16/06

Alan J. Morrison Date
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